PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 97-022-D1-CO)

IN THE APPLICATION OF:	)		
	)		
Rubin, *et al.*	)		
	)		
Serial No. **10/685,737**	)	Examiner:	**Skibinsky, A. L.**
	)		
Filed: **October 15, 2003**	)	Group Art Unit:	**1631**
	)		
Title **A System for Cell-Based Screening**	)	Confirmation No.:	**6145**

APPELLANTS' BRIEF IN SUPPORT OF THE APPEAL TO THE BOARD OF PATENT APPEAL AND INTERFERENCES

Dear Sir:

This Appeal Brief is submitted pursuant 37 C.F.R. 41.37, within two months from the November 10, 2008 filing of the Notice of Appeal. If additional fees are due the Commissioner is authorized to charge our deposit account number 13-2490.

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I. Real Party in Interest

The real party in interest is Cellomics, Inc., the assignee of record, which is a subsidiary of Thermo Fisher Scientific.

II. Related Appeals and Interferences

There are no related Appeals and Interferences.

III. Status of Claims

Claims 40-48 are pending in this application. Claims 40-48 are being appealed. Of these claims, claim 40 is independent. A clean set of the pending claims is attached in the Claims Appendix beginning at page 10. As indicated in the Claims Appendix, claims 1-39 are cancelled.

Claims 40-48 were finally rejected in the Final Office Action mailed June 10, 2008. A Notice of Appeal was filed via EFS on November 10, 2008. This Appeal Brief is being filed within two months of the filing of the Notice of Appeal.

IV. Status of Amendments

No claims have been amended or canceled in the instant brief.

V. Summary of Claimed Subject Matter

Claim 40, the sole independent claim, relates to a computer readable storage medium which comprises instructions for causing a cell screening system to execute procedures for measuring internalization of cell surface receptor proteins in individual cells on an array of locations which contain multiple cells. The procedures comprise identifying internalized cell surface receptor proteins in multiple individual cells wherein the individual cells comprise at least a first luminescent reporter molecule that labels a cell surface receptor protein of interest resulting in a labeled cell surface receptor protein, and at least a second luminescent reporter molecule that reports on cells, wherein the identifying comprises determining whether luminescent signals from the labeled cell surface receptor protein in the individual cells identified by the at least second luminescent reporter molecule meet or surpass a user-defined threshold luminescent

intensity, wherein luminescent signals from the labeled cell surface receptor protein that meet or surpass the user-defined threshold luminescent intensity represent an internalized cell surface receptor protein. The procedures further comprise calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein wherein the calculations provide a measure of internalization of the cell surface receptor protein in the individual cells; and displaying data on the measure of internalization of the cell surface receptor protein in the individual cells. See Applicant's specification *inter alia* page 12, line 22 through page 13, line 10; page 45, line 8 through page 46, line 5; Example 3, page 51, line 8 through page 61, line 14.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 40-42 and 44-48 are unpatentable under 35 U.S.C. § 103(a) over Marks et al, in view of Kallal et al in further view of Proffitt et al.
2. Whether claim 43 is unpatentable under 35 U.S.C. § 103(a) over Marks et al, in view of Kallal et al in further view of Proffitt et al as applied to claims 40-42 and further in view of Dunlay, et al.

VII. Argument

There are only two remaining rejections of claims 40-48. Claims 40-42 and 44-48 are rejected under Marks et al, in view of Kallal et al in further view of Proffitt et al. Claim 43 is rejected under 35 U.S.C. § 103(a) as obvious over Marks et al, in view of Kallal et al in further view of Proffitt et al as applied to claims 40-42 and further in view of Dunlay, et al..

Applicants respectfully assert that the Patent Office's rejection does not meet the statutory standard required for an obviousness rejection under 35 U.S.C. §103(a). The reasons supporting patentability are set forth below.

A. The Office Erred in Rejecting Claims 40-42 and 44-48 under 35 U.S.C. § 103(a) as being obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al.

Claims 40-42 and 44-48 stand rejected as obvious over Marks, et al, in view of

Kallal, et al in further view of Proffitt, et al. For the following reasons, the Applicants respectfully traverse.

i. The cited references alone or in combination do not teach or disclose all of the claim limitations

In order to establish a *prima facie* case of obviousness the Patent office must establish that the prior art references alone or in combination must teach or suggest ***all*** the claim limitations. MPEP § 706.02(j).

The references alone or in combination do not teach, suggest, or make obvious all of the claim limitations of presently pending claim 40.

Presently pending claim 40 recites as follows:

> A machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for measuring internalization of cell surface receptor proteins in individual cells on an array of locations which contain multiple cells, wherein the procedures comprise:
>
> a) identifying internalized cell surface receptor proteins in multiple individual cells on the array of locations, wherein the individual cells comprise at least a first luminescent reporter molecule that labels a cell surface receptor protein of interest resulting in a labeled cell surface receptor protein, and at least a second luminescent reporter molecule that reports on cells, wherein the identifying comprises determining whether luminescent signals from the labeled cell surface receptor protein in the individual cells identified by the at least second luminescent reporter molecule meet or surpass a user-defined threshold luminescent intensity, wherein luminescent signals from the labeled cell surface receptor protein that meet or surpass the user-defined threshold luminescent intensity represent an internalized cell surface receptor protein;
>
> b) **calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein wherein the calculations provide a measure of internalization of the cell surface receptor protein in the individual cells**; and
>
> c) displaying data on the measure of internalization of the cell

surface receptor protein in the individual cells.

As admitted by the Patent Office in the rejection mailed June 10, 2008, "Marks in view of Kallal et al. does **not** teach calculating a number and or percent of the individual cells that internalized the at least first luminescently labeled reporter molecule." The Patent Office then asserts that Proffitt et al. cures this deficiency by teaching "a computerized scanning system and algorithm that is able to measure the relative cell numbers that contain a florescent label." The Patent Office further states that in Proffitt et al, "[t]he total relative fluorescence intensity for the entire well containing cell is determined…" While Proffitt is asserted to cure the deficiencies of Marks et al in view of Kallal et al. the Patent Office does not assert that Proffitt et al teaches "calculating a number and or percent of the **individual cells** that internalized the at least first luminescently labeled reporter molecule," but instead the Patent Office admits that Proffitt et al teaches calculating the intensity of the "entire well" and measures "the relative cell number." Thus, as admitted by the Patent Office, Proffitt et al does **not** actually teach the stated claim limitation, as Proffitt et al does **not** teach measuring fluorescence from individual cell, but rather teaches a homogeneous assay, in which the fluorescence from the entire well is measured and then adjusted to get a measurement of the relative cell numbers. Thus, Proffitt et al, in fact, does **not** cure the deficiencies of the other references.

The Patent Office goes on to assert in the Action mailed June 10, 2008 that:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the procedure of labeling the internalizing receptor a [*sic*] fluorescent protein as taught by Marks in view of Kallal et al and then measuring the number of cells that had the internalized fluorescent protein with the computerized scanning system as taught by Proffitt et al. One of skill in the art would have been motivated to use the cell quantifying fluorescently labeled cells as taught by Proffitt et al to measure the internalization of cell surface receptors as taught by Marks in view of Kallal et al.

However, as argued above, Proffitt teaches looking at the total fluorescence of the collection of cells in the well and then determining relative cell number. Proffitt does not teach calculating a number and or percent of the **individual cells**. Thus, contrary to the Patent Office's assertion, it would be impossible to "measure[ing] the number of cells

that had the internalized fluorescent protein" using the methods of Proffitt, since Proffitt teaches looking at the total fluorescence of the collection of cells in the well.

Assuming that Marks in view of Kallal teach labeling an internalizing receptor fluorescent protein, as asserted by the Patent Office, these labeled internalizing receptor proteins would fluoresce both when the receptor was localized to the plasma membrane and when it was internalized. Thus, using the measurement methods taught by Proffitt, which teaches looking at the total fluorescence of the collection of cells in the well, would result in an inability to distinguish between cells in which the receptor has internalized and cells in which the receptor is localized to the cell surface. In both circumstances the cell would emit the fluorescence and the methods of Proffitt would simply look at total fluorescence from the well. Thus, given the methods of Proffitt, it is not possible to calculate **"a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein** as recited in the instant claims; and, as admitted by the Patent Office, Marks in view of Kallal does not teach this claim limitation either. Therefore, the combination of Marks in view of Kallal and further in view of Proffitt do not teach "calculating **a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein"**

Thus, the combination of references cited by the Patent Office does not teach or suggest machine readable storage media for identifying internalized cell surface receptor proteins in multiple **individual cells** and calculating a number and/or percent of the **individual cells that internalized the labeled cell surface receptor protein** wherein the calculations provide a measure of internalization of the cell surface receptor protein in the **individual cells** and thus the Patent Office has not established a *prima facie* case of obviousness with respect to the invention of independent claim 40. Since the remaining claims all depend from claim 40, it is also clear that the Patent Office has not established a *prima facie* case of obviousness with respect to them.

Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejection.

B. The Office Erred in Rejecting Claim 43 under 35 U.S.C. § 103(a) as being obvious over Marks, et al, in view of Kallal, et al in further view

of Proffitt, et al. as applied to claims 40-42 and further in view of Dunlay, et al.

Claim 43 stands rejected as obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al as applied to claims 40-42 and further in view of Dunlay, et al. For the following reasons, the Applicants respectfully traverse.

i. The cited references alone or in combination do not teach or disclose all of the claim limitations

In order to establish a *prima facie* case of obviousness the Patent office must establish that the prior art references alone or in combination must teach or suggest ***all*** the claim limitations. MPEP § 706.02(j).

Claim 43 is dependent on claim 40 and thus shares all of the claim limitations of claim 40. Marks et al in view of Kallal et al in further view of Proffitt do not teach, suggest or make obvious all of the claim limitations of claim 40 as outlined above in section A. The addition of Dunlay et al. does not cure the deficiencies of Marks et al, Kallal et al and Proffitt et al as applied to claim 40 and thus, the combination of all of the references does not teach suggest or make obvious the claim limitations of pending claim 40 or its dependent claim 43. Thus, it is clear that the Patent Office has not established a *prima facie* case of obviousness with respect to the invention of independent claim 40, nor the dependent claims, including claim 43. Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejection.

C. Conclusion

In summary, the presently claimed methods cannot be rendered obvious by Marks, et al, in view of Kallal, et al in further view of Proffitt and further in view of Dunlay et al because Marks, et al alone or in combination with all of the further references does not teach all the elements of the presently pending claims. The combination of Mason et al. in view of Kallal et al and Proffitt et al provides no teaching or suggestion regarding methods or machine readable storage media for identifying internalized cell surface receptor proteins in multiple **individual cells** and calculating a number and/or percent of the **individual cells that internalized the labeled cell surface receptor protein** wherein the calculations provide a measure of internalization of the cell surface receptor protein in the **individual cells.** Accordingly, the Applicants respectfully

submit that this rejection is improper.

Respectfully Submitted,

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/Isadora F. Bielsky/

Isadora F. Bielsky, Ph.D.
Registration No. 60,748

McDonnell Boehnen
Hulbert & Berghoff LLP
300 South Wacker Drive, 31st Floor
Chicago, IL 60606

Telephone: 312.913.0001
Facsimile: 312.913.0002

VIII. CLAIMS APPENDIX

1. (Canceled)

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Canceled)

7. (Canceled)

8. (Canceled)

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (Canceled)

21. (Canceled)

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. (Canceled)

37. (Canceled)

38. (Canceled)

39. (Canceled)

40. (Previously presented) A machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for measuring internalization of cell surface receptor proteins in individual cells on an array of locations which contain multiple cells, wherein the procedures comprise:

a) identifying internalized cell surface receptor proteins in multiple individual cells on the array of locations, wherein the individual cells comprise at least a first luminescent reporter molecule that labels a cell surface receptor protein of interest resulting in a labeled cell surface receptor protein, and at least a second luminescent

reporter molecule that reports on cells, wherein the identifying comprises determining whether luminescent signals from the labeled cell surface receptor protein in the individual cells identified by the at least second luminescent reporter molecule meet or surpass a user-defined threshold luminescent intensity, wherein luminescent signals from the labeled cell surface receptor protein that meet or surpass the user-defined threshold luminescent intensity represent an internalized cell surface receptor protein;

b) calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein wherein the calculations provide a measure of internalization of the cell surface receptor protein in the individual cells; and

c) displaying data on the measure of internalization of the cell surface receptor protein in the individual cells.

41. (Previously presented) The machine readable storage medium of claim 40, wherein the individual cells are live cells, and wherein steps (a) and (b) are performed at multiple time points.

42. (Previously presented) The machine readable storage medium of claim 40, wherein the procedures further comprise determining one or more of the following:

i) an aggregate area of the objects that represent the internalized cell surface receptor protein;

ii) an aggregate intensity of the objects that represent the internalized cell surface receptor protein;

iii) a normalized aggregate intensity of the objects that represent the internalized cell surface receptor protein;

iv) a number of objects that represent the internalized cell surface receptor protein; and

v) an average number per cell of objects that represent the internalized cell surface receptor protein.

43. (Previously presented) The machine readable storage medium of claim 40, wherein the procedures comprise:

i) obtaining a low resolution image to identify locations in the array of locations that contain internalized cell surface receptor proteins; and

ii) obtaining a high resolution image of only those locations that contain internalized cell surface receptor proteins as determined in step (i).

44. (Previously presented) The machine readable storage medium of claim 1 wherein the first luminescent reporter molecule comprises a fluorescent protein.

45. (Previously presented) The machine readable storage medium of claim 1 wherein the first luminescent reporter molecule comprises an antibody.

46. (Previously presented) The machine readable storage medium of claim 1 wherein the first luminescent reporter molecule comprises a fluorescent reporter molecule.

47. (Previously presented) The machine readable storage medium of claim 1 wherein the second luminescent reporter molecule comprises a fluorescent reporter molecule.

48. (Previously presented) The machine readable storage medium of claim 1 wherein the cell surface receptor protein is a G-protein coupled receptor.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.